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## Edinburgh Research Explorer

### **The impact of bilingualism on cognitive functions across the lifespan and in brain diseases**

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## Focused Workshop

Saturday, 28 May

### Focused Workshop 1

Advanced imaging methods for the assessment of MS pathogenesis and treatment

#### FW01-1

##### Insight into the pathogenesis of multiple sclerosis using metabolic imaging

O. Ciccarelli

*London, United Kingdom*

The mechanisms that underlie the pathogenesis of multiple sclerosis (MS) are partially understood, and include inflammatory demyelination, oxidative stress, mitochondrial dysfunction, glutamate excitotoxicity, sodium homeostasis imbalance, neuroaxonal degeneration and gliotic response. These mechanisms lead to pathological abnormalities, which are responsible for acute and progressive disability.

Metabolic imaging comprises techniques that exploit the magnetic resonance properties of atomic nuclei, such as protons or sodium ions. These techniques include <sup>1</sup>H-Magnetic Resonance Spectroscopy (MRS) and Sodium Imaging. I will describe the insights into the pathogenesis of MS which have been provided by MRS and Sodium imaging studies. These studies have suggested mitochondrial metabolic dysfunction and neuroaxonal loss at the onset of acute events, in relapsing remitting MS and in the early stages of primary progressive MS, increased mitochondrial activity after acute MS lesions, raised total sodium concentration within and outside lesions (especially in progressive MS), reduced concentration of GABA in the hippocampus and sensorimotor cortex in patients with progressive MS than healthy controls, increased glutamate levels in acute lesions and normal-appearing white matter, abnormalities in the glutamatergic pathways in the cervical cord of early primary progressive MS (in the absence of extensive spinal cord atrophy), and glial activation in T2 lesions and normal-appearing white matter. Clinical translation of metabolic imaging techniques may be useful to answer key questions on the pathogenesis of MS. Further technical developments aim at improving the sensitivity and specificity of these techniques and at translating them to clinical trials.

**Disclosure:** OC serves as a consultant for Biogen, Genzyme, Roche, GE Healthcare and Novartis (payments are made to the institution); she receives an honorarium as Associate Editor of Neurology; she receives research funding from EPSRC, UKMSS, NMSS, NIHR ULCH BRC and UCL.

#### FW01-2

##### The promise of ultra high field MRI in multiple sclerosis

F. Barkhof

*Amsterdam, The Netherlands*

There is a continuous quest to move MR imaging to higher fields strengths as this improves the signal-to-noise ratio (SNR). In terms of clinical applications, field strength moved from low field (0.5 Tesla) to high field (3T), as reviewed in *Neuroradiology* (2009;51:279-292). More recently, so-called ultra-high field (7T) scanners have become available for whole body imaging and has been approved by regulators for human applications. MRI at 7T provides challenges in terms of signal homogeneity, artefacts and limitations in terms of RF deposition, which are being overcome slowly. It is an interesting research tool that offers new possibilities for niche applications such as improved detection of cortical lesions (*Brain*. 2016 Mar 8. pii: aww037. [Epub ahead of print]), which are particularly extensive in progressive MS (*Neurology*. 2015 Nov 10;85(19):1702-9). The higher SNR can also be used to study small structures such as the hippocampus, hypothalamus. Due to susceptibility artefacts around osseous structures, imaging at 7T in the optic nerve and spinal cord is quite challenging. The enhanced susceptibility effects at 7T within veins and lesions with iron accumulation however is advantageous and helps to differentiate MS from other disorders such as Susac syndrome (*Mult Scler*. 2012 Nov;18(11):1592-9) and NMO (*AJNR Am J Neuroradiol*. 2016 Mar 24).

**Disclosure:** Consultancy agreements with Roche, Novartis, Biogen, Genzyme, Synthon, TEVA. Research support to my group from Toshiba, Philips, Novartis, TEVA.

## FW01-3

### Assessing tissue damage and repair in multiple sclerosis by positron emission tomography

B. Stankoff

*Paris, France*

Positron emission tomography, a quantitative nuclear medicine technology that uses labeled compounds recognizing specific biological targets, offers the unique opportunity to directly assess some key mechanisms involved in MS pathophysiology. Several stilbene and benzothiazole derivatives have been repurposed for the dynamic imaging by PET of myelin loss and repair in the MS brain. Robust non-invasive quantification techniques were validated and recently allowed to perform longitudinal studies *in vivo*. A great heterogeneity in individual remyelination potential was shown during the relapsing remitting phase of the disease, with a close correlation between remyelinating ability, neurodegeneration and neurological disability. The most popular target for PET microglial imaging is the TSPO macromolecular complex, which is drastically up-regulated in activated microglial cells. PET with the reference compound [11C]-PK11195 identified diffuse microglial activation in the normal appearing white matter and in the cortex of patients with a progressive form of MS. To circumvent some weaknesses of this tracer, a range of improved second-generation TSPO ligands has been developed, and novel fluorinated compounds should now allow to disseminate this imaging technology to many centres. The central benzodiazepine receptor antagonist 11C-Flumazenil (FMZ) is an imaging marker of neuronal integrity, and has been used to quantify and regionally map the neuronal component of grey matter damage in MS, both at the group level and at the individual level. The combination of these imaging probes with MRI sequences will enable to detangle several key pathophysiologic mechanisms that drive disability in MS, and will contribute to the development of new therapies.

**Disclosure:** Nothing to disclose.

## Focused Workshop 2

### Genetic approaches in neuropathies

## FW02-1

### Genotype-phenotype correlations in hereditary neuropathies

M. Auer-Grumbach

*Graz, Austria*

Hereditary neuropathies are clinically and genetically very heterogeneous with more than 60 genes identified so far. The classical and most common form is Charcot-Marie-Tooth disease (CMT, also known as motor and sensory neuropathy, HMSN), which is characterized by slowly progressive weakness and wasting in the distal parts of upper and lower limbs, symmetric foot-deformities and variable sensory disturbances. The underlying pathological event is demyelinating (primarily affecting Schwann cells, CMT1) or axonal (primarily affecting axons, CMT2) nerve damage. Phenotype-genotype correlation studies have shown, that some genetic subtypes are associated with a particular phenotype. Knowledge of additional features such as vocal cord paralysis, scoliosis, optic atrophy, hearing loss, and ulcero-mutilating features amongst others often serves to a definite genetic diagnosis. Mutations in known CMT genes leading to such complicated phenotypes of hereditary neuropathies will be discussed in detail based on case reports.

**Disclosure:** Nothing to disclose.

## FW02-2

### Whole-exome sequencing in patients with inherited neuropathies: outcome and challenges

J. Baets

*Antwerp, Belgium*

The genetic diversity of inherited neuromuscular disorders such as inherited peripheral neuropathies is extensive and recently the more widespread use of next generation sequencing (NGS) technologies and most notably whole-exome sequencing (WES) has accelerated gene discovery and genetic diagnosis. Although traditional genetic strategies were more bound to the lines of previously established knowledge, WES and is powerful enough to be truly “disruptive” by rapidly yielding large quantities of unbiased genetic data. Genetic heterogeneity now turns out to be much more extensive. Expanding disease spectra break up the boundaries between disease entities and pressurize existing genotype-phenotype correlations to the point of making them unintelligible. The unexpected identification of (spurious) variations in known and novel genes is puzzling. A huge task still waits to establish the causal links between this overabundance of genetic variation and disease. Still, the absence of a precise genetic diagnosis in patients precludes genetic counselling, pre-implantation genetic diagnosis and ultimately therapy. At

the same time WES is an extremely powerful tool as it holds the promise of fully saturating the causal genetic map of Mendelian disease.

**Disclosure:** Nothing to disclose.

## FW02-3

### New opportunities of therapy in genetic neuropathies

D. Pareyson

*Milan, Italy*

There is still no effective drug treatment for Charcot-Marie-Tooth (CMT) and related neuropathies. A Cochrane review of the six randomised controlled trials (RCTs) performed with ascorbic acid confirms that the drug is not effective in adults and children with CMT1A. Promising therapeutic approaches for different CMT types, based on cellular and animal model data, include: progesteron antagonists, high-throughput screening for compounds down-regulating PMP22 expression, regulators of unfolded protein response and endoplasmic reticulum stress, Histone Deacetylase 6 Inhibitors, modulators of neuregulin pathways, of GABA-B receptor and of P2X7 receptor. PXT3003, a fixed combination of low doses of baclofen, naltrexone hydrochloride and sorbitol, has been tested in CMT1A rats and in a phase II RCT in CMT1A patients; a phase III trial is under preparation. It is likely that other RCTs will start soon. L-serine supplementation appears a promising treatment for HSAN 1, associated with mutations in SPTCL1/2. Great advances are being achieved for hereditary amyloidosis associated with transthyretin gene mutations (TTR), for which orthotopic liver transplantation was the only available treatment until recently. TTR stabilizers (Tafamidis meglumine, for adult patients with stage 1 symptomatic polyneuropathy, and diflunisal as an off-label drug) showed encouraging results by significantly slowing disease progression. Oral doxycycline plus tauroursodeoxycholic acid (TUDCA) is another promising approach aimed at both preventing and removing amyloid deposition. TTR gene silencing by means of either small interfering RNA or antisense oligonucleotides proved safe and effective in lowering TTR levels in phase II trials and phase III RCTs for both treatments are ongoing.

**Disclosure:** Nothing to disclose

## Focused Workshop 3

### Addressing quality of care for neurological patients

## FW03-1

### Optimising quality of care in epilepsy

E. Ben-Menachem

*Gothenburg, Sweden*

The key to improving quality care is to improve access to epilepsy centers and the facilities that they offer. It is important that when offering treatment for epilepsy the patient becomes a partner in care with access to as much information as possible about the disease and prognosis and possibilities of treatment. Quality of care means access to: Appropriate diagnostic capabilities delivered in a timely fashion. (1 or more EEG, MRT, possibly CSF when applicable, detailed history, physical exam, in difficult cases genetic testing, autoimmune analysis, if applicable). Lack of availability of video-EEG (vEEG) facilities will decrease the possibility of optimal care as a diagnosis can be difficult unless seizures are evaluated with a combination of vEEG and ECG. Once a patient has been diagnosed, then treatment is offered. This can vary widely. The quality of care is greatly improved if the physician is well versed in the treatment possibilities for all types of epilepsy. It is usual to start with an antiseizure drug before going on to more advanced treatment options. If a patient does not become seizure free after 2-3 appropriate antiseizure drugs, then a new diagnostic evaluation should be done and other options such as epilepsy surgery considered. All along the support of a trained epilepsy nurse improves patient care by creating almost constant access to a professional when encountering social problems involved with epilepsy as well as a person whom to immediately report possible side effects that can be headed off before becoming serious. Access to a neuropsychologist and a social worker are important in epilepsy care enabling an assessment of cognitive deficits and an evaluation and treatment of psychological comorbidities. An interested psychiatrist is very important but many times not available. Together an epilepsy team will work together with the patient to provide the best care that is currently available. In Europe there are many such facilities, but unfortunately they are not evenly distributed so many patients will not have access to high quality care unless referred to centers specializing in epileptology. It should be the duty of all countries in Europe to strive to broaden the access of expert care to all regions in order to reach every patient. The social and economic gains of improve epilepsy care should make this mission of highest priority in every society.

**Disclosure:** Nothing to disclose.

## FW03-2

### Quality standards of multiple sclerosis service

A. Chaudhuri

*Romford, United Kingdom*

Multiple Sclerosis (MS) is a life-long neurological disease with a high socio-economic burden. There is significant variability in timely diagnosis, treatment and care plan of MS patients. The key components of the proposed Quality Standards of MS service are:

- 1: ACCESS TO A DESIGNATED MS SERVICE: Patients must have access to a specialist neurological service, which should consist of, as a minimum, a consultant neurologist and a specialist nurse.
- 2: EARLY DIAGNOSIS OF MS: Patients are entitled to a timely diagnosis based on contemporary criteria with timely access to investigations (MRI and laboratory tests).
- 3: MANAGEMENT OF MS: There should be ease of access to multi-disciplinary specialist MS clinics for management of relapses and relapse-related symptoms. In addition to pharmacological therapy, a priority should be to improve symptom control and health related quality of life (HRQoL) using patient reported outcome measures (PROMs).
- 4: ACCESS TO APPROVED DISEASE MODIFYING THERAPIES: The treatment decision has to be individualised and take into account patient expectations and preferences while balancing potential benefits against risks of treatment appropriate for life-stage.
- 5: LONG TERM CARE FOR PATIENTS: The comprehensive care plan for MS patients should reach beyond specialist clinics into individual homes, workplaces and social life to deliver the best possible and full quality of life and identify community nursing, rehabilitative, psychological and social resources for continuation of support.
- 6: RESEARCH AWARENESS: Research should be an expected standard of clinical service and MS patients should be made aware of research projects for volunteering and participation.

**Disclosure:** Nothing to disclose

## FW03-3

### Health related quality of life in Parkinson's disease

M. Faber

*Nijmegen, The Netherlands*

Quality of life is a complex construct, and it is difficult to measure. Patients have a unique perspective on what good quality of care constitutes. Knowing this perspective not only empowers professionals to tailor their care to their patients' individual needs, it also strengthens the engagement between patients and their healthcare team. To better capture the patients' perspectives, we developed and validated both a Dutch and a North-American Patient Centeredness Questionnaire for PD (PCQ-PD). Based on experiences of nearly 2,000 patients with Parkinson's disease, 'provision of tailored information' and 'emotional support' could be identified as key elements in the care pathway that needed improvement. This example clearly demonstrates that patient experience scores can serve as a valid and powerful stepping stone for optimization of patient centred care delivery. Another way to encourage patient-centred care is to incorporate patient-reported outcomes (PROMs) into clinical settings. The PDQ-39, i.e. the standardized and disease-specific quality of life measure for Parkinson's disease, is such a PROM. When incorporated into the health care visit, PROMs could fuel conversations between patients and providers that lead to shared decision making and promote the delivery of individualized care. Interviews with patients, neurologists and physiotherapists revealed that the impact highly depends on the presentation format and benchmarks used. In the Netherlands, a routine collection of the PCQ-PD and the PDQ-39 has recently been implemented. The standardized approach allows us to assess the care performance and its impact. During the workshop we will elaborate on the opportunities and challenges that come with this innovation.

**Disclosure:** Nothing to disclose.



## Focused Workshop 4

### Frontier applications in neurosonology

#### FW04-1

##### **Magnetic resonance guided focused ultrasound for neurological disorders**

I. Schlesinger  
*Haifa, Israel*

Magnetic resonance guided focused ultrasound is a new technology that enables intracranial ablation without incisions. The ultrasound rays warm up the tissue through an intact skull creating the lesion with real-time MRI monitoring for localization and thermography. Intracranial tissue is warmed up gradually in a step wise fashion while the patient is awake. If adverse events occur the target can be repositioned before ablation. This technology is being used to treat patients with disabling tremor due to Essential tremor and Parkinson's disease. In these patients, lesioning the ventral intermediate nucleus of the thalamus is effective in relieving tremor with infrequent long term adverse events. Ameliorating central neuropathic pain, reducing motor fluctuations in Parkinson's disease and disruption of the blood-brain barrier have anecdotally been reported and offer a glimpse at possible future applications.

**Disclosure:** Nothing to disclose

#### FW04-2

##### **Ultrasound on the earth and in the orbit**

Z. Garami  
*Houston, USA*

Space adaptation syndrome and visual impairment with increased intracranial pressure (ICP) remain a puzzling problem of astronauts health and missions. These changes define the visual impairment/intracranial pressure (VIIP) syndrome. There are limited pre- and postflight measures to define the risk and even less inflight data is available. The goal of this study was to use multi-equipment ultrasound protocol simultaneously to measure intracranial and extracranial flow patterns (carotid duplex) before an astronauts mission to established baseline data that could provide important information about flow patterns during ICP with and without gravity. Simultaneous, multi-equipment ultrasound testing could be helpful to study cerebral autoregulation and the connection between extra/intracranial flow, as well as arterial/venous flow patterns with and without gravity in cerebrovascular syndromes. VIIP syndrome remains a puzzling problem of astronauts' health and it prevents the planning of longer missions to explore our boundaries in the universe. These observations are also relevant for medical conditions with ICP on Earth. TCD is already a useful tool in detecting vasospasm and occlusion in our every day practices but there is still room for improvement when dealing with unrecognized and underdetected ischemia and hypoperfusion after stroke, intracerebral or subarachnoid, and cerebellar hemorrhages.

The danger of intracranial hypertension is frequently underestimated, especially in stroke patients. In many cases, ICP is not monitored, and it may cause severe secondary insults by unrecognized ICP elevation. Therefore, non invasive ICP assessment tools and methods developed for NASA could be a helpful tool for our patients, too.

**Disclosure:** Nothing to disclose.

#### FW04-3

##### **The unstable carotid artery plaque**

D. Russell  
*Oslo, Norway*

Carotid plaque characteristics can help to identify those patients with a relatively higher risk for stroke and help select patients who may benefit from intervention over medical treatment alone. Echolucent plaques are thought to be more unstable than echo-rich plaques. Shear wave elastography provides information about plaque stiffness and a better correlation to histology compared to GSM assessments. 3D imaging has been used in volumetric measurements and the detection of plaque ulceration. Ultrasound contrast agents are helpful in detecting plaque surface irregularities and plaque neovascularization. Superb microvascular Imaging is a new ultrasound image technique (Toshiba Medical Systems) that allows the visualization of very small low-flow signals from small blood vessels in the plaque without the use of contrast agents. Symptomatic patients with microembolic signals, assessed by TCD, have a higher risk for developing ipsilateral stroke. MRI detects intraplaque hemorrhage, lipid-rich core, calcification, the fibrous cap and ulceration. Dynamic contrast-enhanced MRI allows assessment of plaque neovascularization. Patients with silent cerebral ischaemic events have a higher risk of future stroke. Positron emission tomography (PET) imaging assesses specific metabolic functions with tracers labelled with positron emitting radio-isotopes. PET with <sup>18</sup>Ffluorodeoxyglucose can probe plaque inflammation in unstable plaques directly. Biomarkers have been shown to improve prediction independent of conventional risk factors and a recent study suggests that gamma-butyrobetaine (gamma-BB) and its precursor trimethyllysine (TML) may predict cardiovascular mortality. Application of plaque imaging in prospective studies will hopefully, in the near future, tell us how we can best guide treatment, especially in asymptomatic patients.

**Disclosure:** Nothing to disclose.

## Focused Workshop 5 Abnormal movements in sleep

### FW05-1

#### Regulation of motor control during sleep

P.-H. Luppi

*Lyons, France*

Paradoxical sleep (PS) is characterised by muscle atonia induced by ponto-medullary-spinal pathways. It was first demonstrated that a pontine area recently named sublaterodorsal tegmental nucleus (SLD) contains the neurons inducing the muscle atonia of PS. Besides, it was shown that glycine induces the hyperpolarization of motoneurons during PS. We recently define in detail the network responsible of muscle atonia during PS combining Fos staining, retrograde tracing and immunohistochemistry or “in situ” hybridization of markers of cholinergic, glutamatergic, GABAergic and glycinergic neurons. We showed that glutamatergic neurons localized in the SLD triggered muscle atonia during PS by means of their descending projections to GABA/glycinergic neurons localized in the ventral medullary formation namely the ventral gigantocellular reticular nucleus (GiV). We further showed that these neurons project to the spinal cord and are activated during PS. To directly demonstrate the role of these glutamate and GABA/glycinergic neurons in PS atonia, we inactivated SLD glutamatergic or GiV GABA/glycinergic transmission using transfection with AAVs of short hairpin RNA specific of the mRNAs of the vesicular glutamate 2 (vGLUT2) or GABA/glycine vesicular (vGAT) transporters. These animals display absence of atonia and large movements during PS confirming the role of the SLD glutamatergic neurons and the GABA/glycinergic neurons in the induction of muscle atonia during PS. In line with these results, we propose that REM sleep behavior disorder (RBD) is due to a specific degeneration of PS-on glutamatergic neurons localized in the SLD or the glycinergic/GABAergic premotoneurons localized in the GiV. Conversely, cataplexy in narcoleptic would be induced by a recruitment of the SLD neurons by a neuronal network regulating emotion.

**Disclosure:** Nothing to disclose.

### FW05-2

#### Simple motor movements

A. Iranzo

*Barcelona, Spain*

Sleep is a physiological state characterized by reduced bodily movement. However, healthy people, particularly young persons, may display non pathological simple manifestations like facial grimaces, minor jerks, and isolated behaviors such as kicking, slapping and sobbing. These “normal” behaviors may occur during the transition from wakefulness to sleep (e.g., hypnic starts), nonREM sleep (e.g. sleep talking) and REM sleep (e.g., head myoclonus, repetitive movements of the feet and hands). In addition, the following pathological conditions may present with simple motor events. REM sleep behavior disorder. In addition to complex behaviors like punching or jumping out of bed, patients present simple manifestations such as jerks, grimaces, kissing, laughing or waving arms. NONREM sleep parasomnias. In addition to complex behaviors occurring in sleepwalking and night terrors patients may present confusional arousals where they simply open their eyes, look around, mutter and sit up in bed. Nocturnal frontal lobe epilepsy. Besides dystonic postures and wandering patients may display minor events called paroxysmal arousals consisting in body jerks and raising the head and sit on bed. Hypnagogic foot tremor. Series of rhythmic and fast movements of the whole foot during light sleep. Periodic leg movements in sleep. These movements may be minor, asymptomatic, and only involving the foot and ankle. Restless legs syndrome. Patients may show foot tapping to alleviate their unpleasant leg sensations during wakefulness. Cataplexy. Some cataleptic events may be minor only involving the head or the knees during few seconds.

**Disclosure:** Nothing to disclose.

## FW05-3

**Complex motor movements**R. Khatami*Barmelweid, Switzerland*

Motor symptoms during sleep comprise a spectrum of paroxysmal phenomena that lead to sleep disruption, sleep fragmentation and eventually contribute to excessive daytime sleepiness. According to the International Classification of Sleep Disorders (ICSD-III) paroxysmal motor phenomena during sleep include parasomnias, sleep-related movement disorders, epilepsies and isolated symptoms. This workshop aims at characterizing the clinical features, etiology, electrophysiological features and treatment of complex motor behavior occurring during NREM-sleep, REM sleep or sleep state transitions. Starting from video presentations the semiology of typical and atypical features will be introduced. Complex motor symptoms may present as repetitive movements or semi-purposeful often stereotyped behavior. Specific forms include violent behaviors leading to self-injuries or harmful behavior directed to others. Clinical and electrophysiological features will be added to further characterize the underlying pathophysiology. The workshop will show that complex motor behaviors are not necessarily a unitary phenomenon, but should rather be considered as the manifestation of a variety of different diseases, as exemplified by cases of arousal disorders, nocturnal frontal lobe epilepsy and psychiatric disorders. Thus, careful examination and extended diagnostic workup is needed for proper diagnosis of underlying disease and adequate treatment.

**Disclosure:** Nothing to disclose.

## Focused Workshop 6

**New concepts about language processing in the brain**

## FW06-1

**The dual-loop model and aphasia**C. Weiller*Freiburg, Germany*

A dual-loop model for the processing of language in the brain was proposed early in history and has also formed the basis for many neuropsychological models. These models incorporate a (direct) route for sensorimotor mapping and a (indirect) route for “semantic” processing. Dual-loop models also emerged in the field of visual processing, motor control, or spatial attention. Thus, a general dual-loop system emerges as a framework for the interpretation of cognition in human brains independent of the modality. Modern imaging techniques like Diffusion-Tensor-Imaging (DTI) based fibre tracking identified several long human association tracts for ventral and dorsal pathways. The extreme capsule (EmC)/IFOF and uncinate fascicle (UF) are part of the ventral system, and the superior longitudinal fasciculi (SLF II, III) and the arcuate fasciculus (AF) are all dorsal pathways. This talk reviews language processing in the brain in the context of a domain general dual-loop system on basis of imaging studies in normal subjects and patients with aphasia. In short: speech production is a dorsal stream task, while comprehension requires the ventral stream. At the acute stage, Wernicke’s aphasia (posterior STG/MTG) and Broca’s aphasia (mainly inferior frontal gyrus (IFG) map to defined brain regions affecting both streams, thus explaining phonological (d) and semantic (v) paraphasias and comprehension problems (v) in Wernicke’s and agrammatism in Broca’s aphasia, as the IFG comprises the necessary interaction node for the two stream to extract structure from a sequence, a prerequisite for syntax processing.

**Disclosure:** Nothing to disclose.



## FW06-2

### The impact of bilingualism on cognitive functions across the lifespan and in brain diseases

T. Bak

*Edinburgh, United Kingdom*

The last decades have witnessed fundamental changes in our understanding of both brain and language. In neurosciences, the static localisationist view of a 1:1 correspondence between circumscribed brain areas and specific cognitive functions gave way to a dynamic interaction of multiple networks, in which the same function can be distributed among many areas and the same area can be part of different networks. In parallel, the concept of language as an autonomous, “informationally encapsulated” module has been superseded by the notion of widely distributed language-related brain networks, going well beyond the traditional language areas and interacting with other aspects of cognition. These advances in the neuroscience of language have been of particular importance for our understanding of bilingualism. Firstly, we came to realise that different languages of a multilingual person cannot be reduced to static representations in isolated brain areas but are subject to parallel activation, inhibition, switching and monitoring within the same brain networks. Secondly, the tension between this parallel activation and a selective output necessary for successful communication constitutes a permanent training for frontal-executive functions. Accordingly, the cognitive effects of bilingualism transcend language itself, leading to a better performance on many executive tasks, particularly those requiring inhibition and switching. This mechanism offers an explanation for a number of recent empirical findings, in which bilinguals were shown to be more resistant to cognitive ageing than monolinguals, develop dementia ca. 4 years later and show a significantly better cognitive recovery after stroke.

**Disclosure:** Nothing to disclose.

## FW06-3

### The writing brain

J.-F. Démonet

*Lausanne, Switzerland*

A vast neural network underpins the functional processing by which the orthographic signal is transformed to motor output; at the neocortical level, these neural territories encompass the upper lateral premotor and parietal cortex. The premotor component, first described by Exner, likely plays a role of buffer interfacing orthographic and allographic components of handwriting. The involvement of the premotor cortex in the non-dominant hemisphere and of transcallosal connections has yet to be specified as well as the role of the superior parietal cortex. The neural correlates of central orthographic processes in handwriting involve “Broca’s area and the posterior temporal cortex in which we observed “dual route” effects, referring to dorsal/ventral processing, respectively involved in sublexical and lexical semantic aspects of orthographic coding. For a review: Planton et al. The “handwriting brain”: a meta-analysis of neuroimaging studies of motor versus orthographic processes *Cortex* 2013 49: 2772-2787

**Disclosure:** Nothing to disclose

**Sunday, 29 May****Focused Workshop 7****Stem cell therapies for the treatment of neurological diseases****FW07-1****Adult Stem Cells for the treatment of multiple sclerosis**A. Uccelli*Genova, Italy*

Adult stem cell treatments are a promising strategy for curing multiple sclerosis (MS). Results obtained from pioneer clinical studies of transplantation of autologous hematopoietic stem cells (AHSC) have demonstrated that this procedure is highly effective in severe forms of MS based on the abrogation of autoreactive clones and reset of the immune system. However, this procedure associates with consistent risks of severe and rarely lethal adverse events. Neural precursor cells (NPC) exert neuroprotective and immunomodulatory effects fostering tissue repair in mice with experimental autoimmune encephalomyelitis (EAE). Similar encouraging results have been obtained in EAE using induced pluripotent stem cells (iPS). However, safety and feasibility issues concerning their transplantation in MS are yet to be addressed. Mesenchymal stem cells (MSC) isolated from the bone marrow or adipose tissues display a significant therapeutic plasticity as reflected by their ability to enhance tissue repair and influence the immune response leading to significant amelioration of EAE. Thus, small clinical trials in MS subjects have demonstrated that MSC administration is safe and provided an early signal of clinical effectiveness. A large phase II multicenter clinical trial is on-going with the aim of demonstrating safety and efficacy of MSC. Overall, current experimental evidence suggests that clinical exploitation of adult stem cells for MS may lead to novel strategies aimed at blocking uncontrolled inflammation, protecting neurons and promoting repair, but not at restoring deranged neural network responsible for irreversible disability.

**Disclosure:** Nothing to disclose.**FW07-2****Stem Cells in muscle diseases**Y. Torrente*Milan, Italy*

Cell therapy is one promising approach to correct genetic diseases by contributing to tissue regeneration; stem cells can be isolated from a healthy donor or, when possible from the same patient. In the first case cells will be transplanted under a regime of immune suppression while in the second case, cells will have to be genetically corrected before transplantation in the same patient from which they were derived. The overall objective of our work is the validation of a clinical treatment for patients affected by Duchenne muscular dystrophy. The project does the groundwork for a phase I/II clinical trial consisting of an intramuscular transplantation of autologous CD133+ stem cells after their engineering through a lentiviral vector. The trial is oriented to DMD boys as Duchenne muscular dystrophy is a X-linked disorder characterized by a mutation in dystrophin gene. Efficacy and possible adverse effects have to be evaluated to test whether this approach may represent a first step towards an efficacious therapy for muscular dystrophy. Our previous works indicated that CD133+ stem cells, a recently identified population of progenitor cells, produce functional improvement upon intra-arterial injection in a mouse model of muscular dystrophy. It thus could be possible to focus on this type of stem cell for autologous transplantation in DMD animal models. Recently transplantation of engineered dystrophic canine muscle-derived CD133+ cells gave promising results in Golden Retriever dystrophic dogs, the most reliable animal model that shows a form of dystrophy very similar to and even more severe than DMD.

**Disclosure:** Nothing to disclose.**FW07-3****Cell transplantation for stroke**S.I. Savitz*Houston, USA*

## Focused Workshop 8

### MDS-ES/EAN: Tics and Tourette syndrome - consensus and controversies

#### FW08-1

##### Challenges in diagnosing tics, Tourette's and comorbidities

K. von Plessen

*Bergen, Norway*

Diagnostic categories within Tic disorders (inclusive Tourette syndrome) include transient, as well as more chronic conditions. Tic disorders are characterized by the presence of tics, which are involuntary contractions of muscles or vocal expressions, but may also compromise more complex behaviors. Tourette syndrome is a relatively frequent and complex neuropsychiatric disease that requires interdisciplinary collaboration between medical professionals, especially because the presence of comorbid conditions is rather the rule than the exception. Comorbidity with Attention-Deficit/Hyperactivity Disorder and obsessive-compulsive disorder is frequent and may pose several diagnostic challenges in young people. A recent European guideline thus recommends the use of a structured diagnostic instrument to screen for other psychiatric diagnoses and specific instruments allowing a dimensional mapping of tics and possible other co-morbid conditions. Besides the most frequent instruments for diagnostic mapping of psychopathology, also current theories and concepts regarding the neurobiological/neuropsychological basis and subsequent adaptation to tics will be presented.

**Disclosure:** Nothing to disclose.

#### FW08-2

##### Tics and Tourette syndrome - Movement disorders or behavioural conditions?

A.E. Cavanna

*Birmingham, United Kingdom*

Patients with Tourette syndrome (TS) show a wide range of clinical presentations, characterised by different levels of severity and complexity. The concept of 'TS spectrum' encompasses conditions characterised by tics only ('pure TS'), tics and complex symptoms such as self-injurious behaviours ('full-blown TS'), tics and co-morbid behavioural problems such as obsessive-compulsive disorder and attention-deficit and hyperactivity disorder ('TS-plus'). Over the last decade, clinical studies using principal component factor analysis and hierarchical cluster analysis have suggested the existence of discrete phenotypes within the TS spectrum. These findings have important implications for the understanding of genotype-phenotype correlations, as well as impact on patients' health-related quality of life and choice of treatment interventions.

**Disclosure:** Nothing to disclose.

#### FW08-3

##### Treatment of tics and Tourette syndrome - Cannabis, deep brain stimulation and beyond

K. Müller-Vahl

*Hanover, Germany*

Tourette syndrome (TS) is a childhood onset neurodevelopmental disorder characterized by multiple motor and one or more vocal tics. The majority of patients suffers, in addition, from psychiatric comorbidities such as attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), depression, anxiety, and self-injurious behavior. Tics most typically start at age 6-8 years, fluctuate spontaneously in the course of the disease, are influenced by different environmental factors, and improve spontaneously in adolescence and young adulthood in the majority of patients. Treatment of patients with TS depends not only on severity of tics, but also the presence and severity of comorbidities. Since it is well known that TS can cause significant impairment in patient's quality of life, in addition, overall social impairment has to be taken into consideration. First-line treatment for tics includes either cognitive behavioral treatment (using habit reversal training or exposure and response prevention training) or pharmacotherapy (using dopamine receptor blocking drugs including aripiprazole, tiapride (in children), sulpiride, and risperidone). However, in most European countries only haloperidol is formally approved for the treatment of tics. Since these substances are not effective in all patients and often associated with significant adverse effects, several other treatment alternatives have we suggested. There is increasing evidence that cannabis-based medication might be such an alternative treatment option that improves not only tics, but also psychiatric symptoms such as ADHD and OCD. In adult, severely affected, and otherwise treatment resistant patients surgical treatment with deep brain stimulation should be taken into consideration.

**Disclosure:** Nothing to disclose.

## Focused Workshop 9

### Focal dementias

#### FW09-1

##### The parietal lobes

J.M. Schott

*London, United Kingdom*

Building on the theme of this focussed workshop, this session will present an overview of the cortical dementias that have a particular predilection for the parietal lobes, using posterior cortical atrophy - sometimes termed the visual variant of Alzheimer's disease - and corticobasal syndrome as the exemplar disorders. Starting with an overview of the anatomy and normal cognitive functions subserved by the parietal lobes, aspects of the history, examination and neuropsychology associated with dominant and non-dominant parietal lobe dysfunction will be illustrated using videos. This will be followed by a discussion of the relevant investigations (imaging and CSF) and the underlying pathology of the neurodegenerative disorders leading to parietal lobe dysfunction.

**Disclosure:** I acknowledge the support of the NIHR Queen Square Dementia BRU, the NIHR UCL/H Biomedical Research Centre, Wolfson Foundation, EPSRC, MRC, ARUK, and EU Horizon 2020. I have received research funding from AVID Radiopharmaceuticals, have consulted for Roche Pharmaceuticals and Eli Lilly, and serve on a Data Safety Monitoring Committee for Axon Neuroscience SE

#### FW09-2

##### The temporal lobes

S.F. Cappa

*Milan, Italy*

Focal degeneration of the temporal lobes is the hallmark of the semantic variant of frontotemporal lobar degeneration. This condition, originally described by Arnold Pick, is most often associated with asymmetric involvement, prevalent on the left side, resulting in a clinical picture of progressive semantic dysfunction characterized by a level of selectivity and a severity of progression, which cannot be observed in any other neurological disease. The study of patients affected by this condition, most commonly due to TDP 43 proteinopathy, has provided unique insights into the neurology of meaning representation. The less common presentation with greater right sided involvement is characterized by a different symptom complex, in which disorders of high order visual processing are often associated with prominent behavioural manifestations. The neuropsychological study of the latter cases is providing complementary insights into the neurology of non-verbal semantics and of social cognitive abilities. Atypical presentations of Alzheimer's disease (AD) can also affect the temporal lobes focally for a prolonged period of time. Also in this case the asymmetry of involvement is a crucial determinant of the neuropsychological features, in term of aphasic (left sided) or visuospatial (right sided) presentations. A selective involvement of the medial temporal lobe is the hallmark of the puzzling condition of hippocampal sclerosis. Often diagnosed as AD in the past, this frequent cause of memory impairment in the elderly population can be associated with a number of degenerative and non degenerative conditions, including TDP 43 pathology.

**Disclosure:** Nothing to disclose

#### FW09-3

##### The frontal lobes

R. Ossenkoppele

*Amsterdam, The Netherlands*

The frontal lobes play an important role in modulating human behavior, cognitive processes and motor function. This presentation focuses on how distinct neurodegenerative conditions (e.g. behavioral variant frontotemporal dementia, non-fluent variant primary progressive aphasia and progressive supranuclear palsy) affect the frontal lobes. More specifically, I will address the clinical syndromes, neuroimaging features and neuropathological changes associated with these diseases. Finally, I will present our studies on the behavioral/dysexecutive variant of Alzheimer's disease.

**Disclosure:** Nothing to disclose.

## Focused Workshop 10

### MDS-ES/EAN: Biomarkers for Parkinson's disease

#### FW10-1

##### The need for better biological markers for PD

W. Poewe  
*Innsbruck, Austria*

Slowing of disease progression remains the single most important unmet need in the treatment of Parkinson's Disease (PD). However, numerous clinical trials over the past 20 years failed or produced inconclusive results. Reasons for such failures include difficulties in choosing clinical endpoints and the lack of reliable biomarkers sensitive to disease progression. In addition, target populations for neuroprotective or disease-modifying trials have been those with early, clinically established PD. Recent research has provided substantial evidence that the pathology underlying PD likely begins years before the first manifestation of classical motor signs of PD. It is therefore conceivable that disease-modifying or neuroprotective interventions targeting the earliest phases of PD might offer greater potential for disease modification as compared to later stages. Idiopathic REM-sleep behavior disorder, hyposmia, depression, constipation have all been associated with an increased risk to later develop classical motor PD and might represent "pre-motor" stages of the illness. Recently a task force of the International Parkinson's Disease and Movement Disorder Society (MDS) has proposed operational research criteria for the definition of prodromal PD. Nevertheless validated biomarkers are needed to enhance sensitivity and specificity of such criteria. The same holds true for early diagnosis as well as measuring disease progression.

**Disclosure:** Nothing to disclose

#### FW10-2

##### Alpha-Synuclein: a new evidence?

W. Meissner  
*Bordeaux, France*

The discovery of alpha-synuclein as the main constituent of Lewy bodies in surviving dopamine neurons in Parkinson's disease (PD) has stimulated research to determine the usefulness of this protein as biomarker for the diagnosis and prognosis of PD. In its physiological form, alpha-synuclein forms an unfolded monomer with a role in vesicle trafficking and recycling. The protein can undergo a multitude of posttranslational modifications including truncation and phosphorylation, and forms aggregates under particular conditions. Oligomers are currently believed to be the most toxic aggregates and seem to have a major role in the underlying neurodegenerative process. Several studies have reported decreased levels of total alpha-synuclein and increased concentrations of oligomers in the cerebro-spinal fluid (CSF) of PD patients compared to healthy controls. Total alpha-synuclein CSF levels were also decreased in patients with multiple system atrophy, suggesting that this marker may not be useful for the distinction between synucleinopathies. Preliminary results of prospective studies further suggest that concentrations of total alpha-synuclein are not changing over time and are not correlated with disease severity. More recent studies have looked at alpha-synuclein levels in more accessible fluids (e.g. blood and saliva) and tissues (e.g. skin, salivary glands and colon biopsies). In this line, preliminary evidence suggests increased plasma concentrations of exosomal alpha-synuclein. These results, together with encouraging findings in tissues, warrant replication and further investigation. The presentation will discuss recent progress and promising future avenues for the development of alpha-synuclein as biomarker in PD and synucleinopathies.

**Disclosure:** Nothing to disclose

#### FW10-3

##### Imaging Markers: MRI

U. Sabatini  
*Rome, Italy*

When magnetic resonance imaging (MRI) was initially introduced in clinical practice, conventional neuroimaging techniques had a marginal role in the diagnosis of Parkinson's disease (PD). The increasing prevalence of PD, partly as a consequence of population ageing, the introduction of experimental therapeutic strategies, and technological advances in MRI have stimulated the development of MRI techniques with a potential for greater sensitivity and specificity for early diagnosis and the quantification of the pathological process. With the introduction of higher field magnets and novel imaging sequences, microstructural, metabolic and functional data is, as never before, contributing to the search for reliable biomarkers of disease progression in PD. Results from existing studies have suggested several MRI-based



measures as potential biomarkers of PD pathology, albeit none of them has yet been identified as a clear winner. These studies converge towards the notion that a single MRI modality cannot be sufficient to characterise the complex pathological mechanisms underlying PD. In fact, multimodal MRI sequences are able to capture tissue characteristics at different scales: macroscopic structure can be assessed through volumetric T1-weighted, microstructural alterations can be detected through diffusion-weighted, iron deposition in specific brain structure can be quantified through R2\* imaging. For this reason, the integration of multimodal MRI indexes is crucial, since they probably carry complementary information regarding the biological process of interest. Datasets in a large cohorts of accurately selected patients, acquired at multiple sites, will grant the opportunity of testing multimodal MRI techniques over large amounts of clinical, neuroimaging and genetic data.

**Disclosure:** Nothing to disclose.

## FW10-4

### Imaging Markers: PET/SPECT

P. Remy

*Créteil, France*

The use of dopaminergic presynaptic ligands such as 18F-DOPA (PET) or cocaine analogues (PET/SPECT) has been used for years to measure the progression of neurodegenerative process in Parkinson's disease (PD). Although several studies have used PET or SPECT to investigate neuroprotective potentiality of several treatments, to date results have been either negative or highly debated. One major issue is to obtain a clinical benefit in patients whose disease has been slowed according to imaging data. Another marker which has been more recently used is the measure of endogenous synaptic dopamine release. Using an 11C-Raclopride displacement method it is possible to demonstrate enhanced dopamine availability in the striatum induced by cell or gene therapy. Eventually, new processes are now investigated to identify alternative markers of PD, such as inflammatory process, using ligand of the TSPO which reveals glial activation. In addition, a ligand of  $\alpha$ -synuclein would be considered as a dramatic improvement in our ability to measure PD degenerative process and to evaluate immunotherapy against  $\alpha$ -synuclein deposition which is already investigated in patients.

**Disclosure:** Nothing to disclose.

## Focused Workshop 12

### Impaired hand function after stroke and peripheral nerve injury: consequences for treatment

## FW12-1

### Treatment of hand function after peripheral nerve injury

J. Valls-Solé

*Barcelona, Spain*

Nerve growth after injury in peripheral nerves is a physiological process. It occurs naturally after the lesion and, although it can be promoted by some drugs such as growth factors, it will occur even in rather adverse situations if the nerve has not lost its continuity. There are many problems with reinnervation: There is a critical window of time in which regeneration must occur for optimal recovery to be achieved. If distal Schwann cells lack axonal contact for a long time, they degenerate, reduce secretion of growth factors, disappear from the bands of Büngner and stop replication, leading to irreversible changes detrimental for functional recovery. It is nowadays impossible to guide the regenerating axons up to the target that they had before the lesion. If nerve regeneration occurs, reinnervating axons may end up innervating a structure different from the one they were innervating before the injury. There are changes at motoneuronal level that make the motoneurons hyperexcitable and respond to inputs from many sources to which they did not respond before the injury. Finally, axon growing means also axonal branching. This provides electrophysiologic studies but also more possibilities of innervation errors and inefficacy of the reinnervated targets. The recovery of hand function depends on all these factors, which are conditioning the rehabilitation progress.

**Disclosure:** Nothing to disclose.

## FW12-2

### Normal and impaired neural coupling of cooperative hand movements

V. Dietz

*Zurich, Switzerland*

In recent years it has become evident that, in a number of functional movements, synergistically acting limbs become task-specifically linked by a soft-wired 'neural coupling' mechanism (e.g. the legs during balancing, the arms and legs during gait and both arms during cooperative hand movements). Experimentally this mechanism becomes elucidated by reflex responses as a marker for a neural coupling. This reflected by the task-specific appearance of reflex EMG responses to non-noxious nerve stimulation, not only in muscles of the stimulated limb, but also, with same long latency, in muscles of meaningful coupled (contralateral) limb(s). After a stroke, nerve stimulation of the unaffected limb during such cooperative tasks is

followed by EMG responses in muscles of the (contralateral) coupled affected limb, i.e. unaffected motor centres influence synergistically acting movements of the paretic limb. In contrast, following stimulation of the affected limb, no contralateral responses appear due to defective processing of afferent input. As a consequence, it may be therapeutically possible to strengthen the influence of unaffected motor centres on the performance of affected limb movements through training of cooperative limb movements required during activities of daily living.

**Disclosure:** Nothing to disclose

## FW12-3

### Bilateral hand movement training after stroke: what is the benefit?

C. Renner

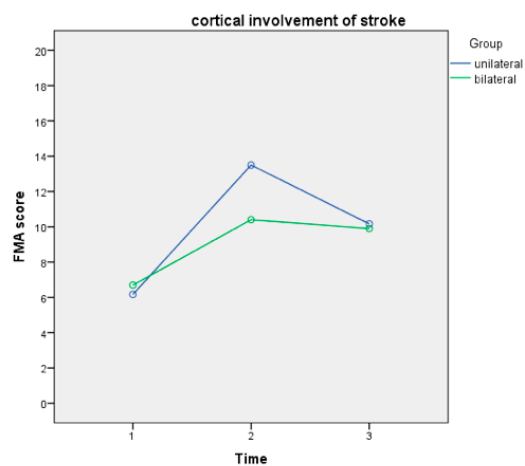
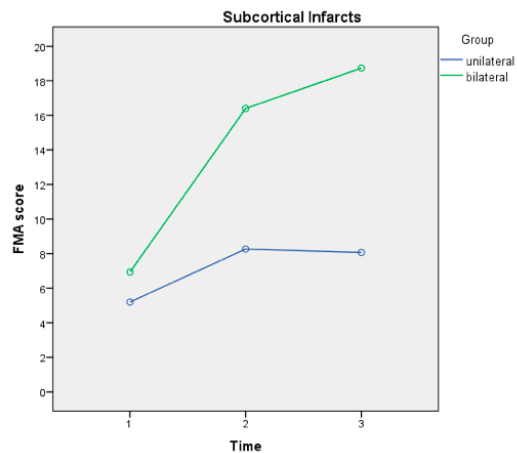
Leipzig, Germany

**Introduction:** Different training strategies have been tested in neurorehabilitation of motor function. Examples include constraint-induced movement therapy (CIMT) and bilateral arm training (BAT). They are based on divergent hypotheses of poststroke reorganization. CIMT promotes activation of the ipsilesional hemisphere counteracting contralesional activation, while BAT involves bihemispheric activation. Yet severely impaired stroke patients unable to move their hands are unable to perform CIMT.

**Methods:** 60 patients with a severe arm paresis were recruited for this randomized single-blinded study and stratified according to lesion location. The bilateral arm training entailed a repetitive training on an “arm-cycle” followed by synchronized bilateral repetitive distal hand training. The unilateral arm training was identical but performed by the paretic limb only. Both trainings were administered twice daily over six weeks and incorporated shaping elements. Main outcome measures included the FMA and biomechanical parameters measuring isometric force and rate of force generation.

**Results:** Both trainings lead to a significant improvement of the FMA and all biomechanical parameters. Patients with pure subcortical stroke, but not patients with cortical involvement of stroke, showed a significantly greater improvement following the bilateral training in FMA ( $p=0.03$ ) and hand extension ( $p=0.02$ ) compared to unilateral training.

**Conclusion:** Bilateral arm training followed by repetitive bilateral hand training leads to greater improvements in motor control and force of the severely paretic upper limb compared to the unilateral training after pure subcortical stroke lesions. These findings may assist in planning different therapeutic regimens in the context of motor impairment severity and lesion location.



**Disclosure:** Nothing to disclose

## Monday, 30 May

### Focused Workshop 13 Sleep and cognition

#### FW13-1

##### Sleep and cognition

P. Maquet

*Liege, Belgium*

Human performance results from an interaction between circadian rhythmicity and homeostatic sleep pressure accumulated during wakefulness. Whether and how this interaction is represented at the level of regional brain responses has not been established. We quantified changes in brain responses to 2 cognitive tasks during 13 functional magnetic resonance imaging (fMRI) sessions scheduled across the circadian cycle during 42h of wakefulness in 33 healthy participants. The temporal profile of cortical responses shows a significant circadian rhythmicity, the phase of which varies across brain regions. Cortical responses also significantly decrease with accrued sleep debt. By contrast, subcortical areas exhibit primarily a circadian modulation, which closely follows the melatonin profile. These results demonstrate a local modulation of brain responses by both circadian rhythmicity and sleep pressure. These results have important bearing on our understanding of sleepiness-related traffic and work accidents, insomnia and rehabilitation programs.

**Disclosure:** Nothing to disclose

#### FW13-2

##### Sleep and emotion

V. Sterpenich

*Geneva, Switzerland*

Recent research has demonstrated that freshly encoded memory traces are replayed during sleep. This mechanism allow information to be integrated into an existing network of representations. During wakefulness, the brain is bombarded with large amounts of information. Thus, to better understand how replay during sleep contributes to memory processes, we need to determine what type of information is prioritized for subsequent replay during sleep. We hypothesized that information with an affective value, which might require long-term behavioral changes, would benefit from offline reprocessing during sleep. Thus, memories of emotionally relevant experiences may have a higher probability of being reprocessed during sleep. Using simultaneous EEG-fMRI recordings, we measured brain activity while healthy participants played alternating blocks of two distinct games, one of which they would eventually win. We also measured brain activity during different sleep stages. Using a neural decoding approach we found that the pattern of brain activity associated with the rewarded game occurs spontaneously during deep sleep and more frequently than the non-rewarded game. In a second experiment, we

artificially reactivated emotional memory traces during sleep using auditory cues in patients with intracranial EEG recordings. We observed that the cues associated with positive events would elicit distinct iEEG responses during sleep in brain regions involved in emotion and memory. Taken together, these findings suggest a general mechanism whereby the brain selectively consolidates memories with a high value for survival. The replay of relevant memories occurs during a physiological state, i.e. sleep, that is highly favorable for neural plasticity.

**Disclosure:** Nothing to disclose

#### FW13-3

##### Sleep and dementia

S. Overeem

*Heeze, The Netherlands*

Alzheimer's disease (AD) is the most common form of progressive dementia. It has been known for a long time that AD patients frequently suffer from sleep disturbances as well as circadian rhythm disorders. In recent years however, evidence is accumulating that suggests a bidirectional relationship between AD and sleep, i.e. sleep disturbances may be a risk factor to develop AD. Several epidemiological studies have shown that sleep restriction increases the risk of cognitive impairment. Experiments in mice showed that sleep deprivation leads to a marked increase in amyloid beta accumulation. Most likely, sleep contributes to the clearance of metabolites such as amyloid beta from the brain. More recently, studies have shown comparable mechanisms in humans. For example, sleep deprivation lead to an increase in cerebrospinal fluid amyloid beta levels in healthy subjects. Besides a link between sleep and amyloid dynamics, other factors may be at play. For example, melatonin may have antioxydant, neuroprotective as well as anti-amyloidogenic effects.

**Disclosure:** Nothing to disclose

## Focused Workshop 14

### Gut microbiota, immunology and neurological diseases

#### FW14-1

##### Microbiota and the gut-brain axis

P. Lepage

*Micalis Institute, INRA, AgroParisTech, Université Paris-Saclay, Jouy-en-Josas, France*

Modifications in the bacterial composition and diversity of the human gut microbiota (microbial dysbiosis) have been associated with digestive tract dysfunctions such as inflammatory bowel diseases. More strikingly, microbial dysbiosis may be associated with pathologies at distance from the intestine and strong evidence, from both human studies and animal models, links intestinal microbiota dysbiosis with metabolic disorders, such as obesity. More recently, associations between microbial imbalances in the gut and neurologic and behavioural disorders have been described in animal models. While some gut microbes have the capability to produce neuromediators that may exert effects in the brain, only sparse data are available in humans and most of them remain highly descriptive. Yet, the possible involvement of the 'microbiota-gut-brain' axis in the development of disorders ranging from autism, multiple sclerosis or depression is currently being investigated. The development of meta-omic technologies that give insight into the functions and potential effect of the non-cultured intestinal bacteria on the host health will surely help understanding how modifications in this finely tuned ecosystem lead to these pathological processes. This may finally lead to the development of new therapeutical approaches to treat and ameliorate these neurological diseases.

**Disclosure:** Nothing to disclose

#### FW14-2

##### Microbiota and CNS autoimmunity (Multiple Sclerosis)

G. Krishnamoorthy

*Martinsried, Germany*

Autoimmunity results from a combined influence of genetic and environmental factors. Emerging evidence in the experimental models of autoimmunity suggests an important contribution of gut microbiota in the disease development. In this presentation, i will present evidence for the role of gut microbiota in mouse models of Multiple Sclerosis, an autoimmune disease of the central nervous system with the special emphasis on how to modulate gut microbiota for therapeutic benefit.

**Disclosure:** Nothing to disclose

#### FW14-3

##### Gut microbiome: a key regulator of neurodevelopment and behaviour

J.F. Cryan

*Cork, Ireland*

The brain-gut-microbiota axis is emerging as a research area of increasing interest for those investigating the biological and physiological basis of neurodevelopmental, age-related and neurodegenerative disorders. The routes of communication between the gut and brain include the vagus nerve, the immune system, tryptophan metabolism, via the enteric nervous system or by way of microbial metabolites such as short chain fatty acids. Studies in animal models have shown that the development of an appropriate stress response is dependent on the microbiota. Developmentally, a variety of factors can impact the microbiota in early life including mode of birth delivery, antibiotic exposure, mode of nutritional provision, infection, stress as well as host genetics. At the other extreme of life, individuals who age with considerable ill health tend to show narrowing in microbial diversity and a proinflammatory phenotype. Stress can significantly impact the microbiota-gut-brain axis at all stages across the lifespan. We have recently shown that fundamental brain processes important for neurological diseases are regulated by the microbiome. These include adult hippocampal neurogenesis and hippocampal expression of BDNF. In the amygdala, germ free animals have increased volume, spine density and morphology, whereas in the prefrontal cortex myelination and myelin-related gene expression is dependent on the microbiome. It has also recently been shown that microglia activation and blood brain barrier integrity are also microbiome-dependent processes. Further studies will focus on understanding the mechanisms underlying such brain effects. Together these data offer the intriguing possibility of therapeutically targeting specific brain processes via the gut microbiome.

**Disclosure:** Nothing to disclose.

## Focused Workshop 15

### Exome sequencing goes bedside: new genes in neurological disorders

#### FW15-1

#### **Cerebellar ataxias: exome sequencing unravels novel genes, false friends and clinical hints for bedside**

M. Synofzik<sup>1</sup>, F. Harmuth<sup>2</sup>, S. Züchner<sup>3</sup>, L. Schöls<sup>1</sup>, P. Bauer<sup>1</sup>, R. Schüle<sup>1</sup>

<sup>1</sup>Tübingen, Germany, <sup>2</sup>Institute of Medical Genetics and Applied Genomics, Tübingen, Germany, <sup>3</sup>Miami, USA

Cerebellar ataxias present a heterogeneous group of degenerative and metabolic diseases. Based on the advances of next-generation sequencing (NGS) techniques such as panel, whole exome sequencing (WES) and whole genome sequencing (WGS), the number of newly identified genetic causes of ataxias is rapidly increasing, with >120 ataxia-associated genes now being identified. This talk will demonstrate that these genetic advances provide unprecedented options to diagnose previously unsolved ataxia patients, to define the genetic basis of many rare and complex ataxia disorders, and to pave the way towards molecular pathways and treatments. In step one, a state-of-the-art overview on NGS findings in ataxias will be provided, including several novel ataxia genes identified by our and other groups. These novel ataxia genes provide insights into underlying pathways, and also putative future biomarkers and treatments. Second, we will show that such NGS results yield not only constructive findings, but also warrant a new level of critical interpretation. NGS and recent related publications deliver a high number of rare variants in known ataxia genes with questionable significance, and flag putatively novel putative ataxia genes which are not yet sufficiently validated. Third, we will show that NGS does not make clinical ataxia expertise dispensable, but, on the contrary, warrants a new level of specific clinical expertise. A high degree of clinical ataxia specialist knowledge is indispensable to reliably interpret the variant lists produced by NGS. Moreover, we will show how clinical hints allow to pinpoint the genetic diagnosis in ataxias even before and without NGS.

**Disclosure:** Matthias Synofzik has received speaker honoraria and research support by Actelion Pharmaceuticals. He was awarded a Else Kröner Memorial Stipend by the Else Kröner-Fresenius Stiftung.

#### FW15-2

#### **Atypical parkinsonian syndromes: rapidly expanding genetic disease spectrum, yet distinct clinical and imaging signatures**

H. Houlden

London, United Kingdom

Parkinsonism is defined by akinesia associated with rigidity or rest tremor. The akinesia can be bradykinesia, hypokinesia or reduced facial expression. There are a variety of causes of parkinsonism, but Parkinson's disease (PD) is the most common. The "atypical parkinsonian syndromes" (called in the past "Parkinson's plus syndromes") are characterized by a rapidly progressive parkinsonism that has a poor or brief response to dopaminergic therapy and often with one or more atypical features that include; early postural instability/autonomic failure, supranuclear gaze palsy, pyramidal or cerebellar signs, alien limb and apraxia. In addition to the usually acquired atypical forms there are an expanding group of inherited parkinsonian syndrome such as the recessive PLA2G6, FBX07, SPG11, PANK2 and other very rare syndromes associated with brain iron where many remain genetically undefined. The diagnostic differentiation of the atypical parkinsonian disorders is essential for both clinical practice and research because the diagnostic tools needed for investigation, prognosis and treatments differ significantly to PD. Atypical parkinsonian disorders have a shorter survival time and more complications. Drug and surgical therapies differ significantly and there are few effective treatments. However, early identification of the different atypical parkinsonian disorders can reduce complications, inform prognosis and allow patients to be enrolled in clinical trials. Genetic testing and imaging signatures are becoming increasingly important tools in which to become adept, and along with clinical skills are essential to the movement disorder specialist in clinical practice and for research.

**Disclosure:** Nothing to disclose



## FW15-3

### **Motor neuron disease and spastic paraplegias: large-scale exome sequencing reveals common pathogenetic hubs**

R. Schüle

*Tübingen, Germany*

Motor neuron disease and hereditary spastic paraplegias (HSP) comprise a heterogeneous group of degenerative diseases affecting the upper and/or lower motor neurons and their axonal projections. The increasing availability and decreasing cost of whole exome sequencing (WES) and whole genome sequencing (WGS) have led to an unprecedented discovery rate of novel genes causing these rare conditions. Despite the genetic heterogeneity, the predilection of motor neurons for the disease pathology and the selective vulnerability of long axonal projections, at least in HSPs, suggest a shared pathophysiology among the genetically defined subtypes of motor neuron disease and HSPs. Discovery of novel disease genes by us and others over the past few years have opened up our view from a gene-centric to a network-centric focus on pathophysiology. In this talk, we will discuss recent advances in genetics of motor neuron disease and HSPs and will highlight how these novel discoveries translate into a better understanding of the cellular mechanisms involved. This mechanistic approach may open up novel therapeutic targets and opportunities.

**Disclosure:** Nothing to disclose.

## Focused Workshop 16

### **Syndromes of central visual and vestibular disorders**

## FW16-1

### **Cortical visual disorders and neglect**

C. Kennard

*Oxford, United Kingdom*

Disorders of the striate and extrastriate cortex lead to a multiplicity of visual disorders which range from a homonymous hemianopia to very specific visual impairments such as prosopagnosia and visuo-spatial neglect. Recent behavioural studies along with functional brain imaging have shed new light on these disorders and in some have offered the prospect for therapeutic interventions. The commonest visual deficit is homonymous hemianopia and several methods have been devised for restoring function either of the visual field itself or by behavioural modification. The current controversy relating to some of these techniques will be discussed. Focal lesions of the extrastriate cortex can lead to specific visual deficits of, for example, colour (achromatopsia), motion (akinetopsia), face (prosopagnosia) and form (visual agnosia) and current views of their functional visual localisation will be described. Visuo-spatial neglect is no longer considered to be a unitary disorder but rather it consists of a number of component deficits, with the precise combination varying from patient to patient, presumably determined by the exact location and extent of brain damage. Mechanisms underlying neglect may not be neglect specific ie they may occur on their own without neglect. Recognition of these component deficits are leading to the introduction of novel therapies such as scanning therapy and hemianopic patching, inducing shifts in spatial representations, prism adaptation and treating non-spatially lateralised deficits pharmacologically.

**Disclosure:** Nothing to disclose.

## FW16-2

### **Peripheral vestibular disorders with essential bedside testing**

B.M. Seemungal

*London, United Kingdom*

## FW16-3

**Central vestibular disorders (from brainstem to cortex)**T. Brandt*Munich, Germany*

The traditional classification of vestibular disorders is based on the anatomical site of the lesion. While it distinguishes between the peripheral and the central vestibular system, certain weaknesses become apparent when applied clinically. For example, peripheral and central lesions may cause similar symptoms such as skew deviation or tilts of perceived vertical which originate with unilateral lesions of graviceptive pathways from the labyrinth and the vestibular nuclei to the midbrain tegmentum and cerebellum. Further, disorders of “higher vestibular function” are missing. A concept of disorders of higher vestibular function is proposed which involve cognition and more than one sensory modality. Three conditions exemplify such higher disorders: room tilt illusion, spatial hemineglect, and bilateral vestibulopathy all of which present with deficits of orientation and spatial memory. Further elaboration of such disorders of higher multisensory functions with respect to lesion site and symptomatology is desirable. The room tilt illusion and spatial hemineglect involve vestibular and visual function to the extent that both conditions can be classified as either disorders of higher vestibular or of higher visual functions. A possible way of separating these disorders in a first step is to determine whether the causative lesion site affects the vestibular or the visual system. For the vestibular system this lesion site may be peripheral or central.

**Disclosure:** Nothing to disclose.

## Focused Workshop 17

**ALS and FTD: two converging diseases?**

## FW17-1

**Neuropathology of FTD and ALS - comparing the patterns of propagation**J. Brettschneider*Philadelphia, USA*

Neurodegenerative diseases share a common pathological hallmark – the accumulation of characteristic proteins into insoluble aggregates in or among selectively vulnerable neurons and glial cells. The disease-related proteins are transformed from their normal conformation into fibrillar or multimeric species that function as seeds and templates to drive non-pathological protein counterparts to adopt a similar structural alteration. Neuropathological studies have identified that stereotypical patterns of pathology occur in various neurodegenerative diseases over time, and that progression of these patterns is associated with increasing severity of the clinical phenotype.

**Disclosure:** Nothing to disclose.

## FW17-2

### Assessment of neuropsychology in ALS and FTD

T. Bak

*Edinburgh, United Kingdom*

Cognitive assessment in patients presenting with motor symptoms faces particular challenges. Patients' performance is determined not only by their cognitive functions but also by their motor impairment: bulbar symptoms influence tasks requiring a verbal response (e.g. naming, verbal fluency) while tasks involving writing or drawing can be compromised by a wide range of motor symptoms, from weakness, through tremor, rigidity, akinesia and dystonia to apraxia. However, most currently available neuropsychological tests assume normal motor performance. Hence, they cannot distinguish whether a low score on a particular task is due to motor or cognitive dysfunction, a crucially important question when assessing the cognitive status. In my presentation, I will discuss examples of the interference between motor and cognitive functions on neuropsychological testing. I will then present a new cognitive screening tool, ECAS (Edinburgh Cognitive Screen for ALS), specifically developed to assess cognitive functions in patients with motor impairment. It has been designed to minimize the influence of motor dysfunction through tasks requiring only minimal motor input such as pointing or yes/no answers. The whole test can be completed in a spoken or a written version. As such, the ECAS allows an adequate cognitive assessment in patients of the ALS/FTD spectrum. I will then present an overview of the neuropsychological studies in ALS/FTD, focusing on the question whether the cognitive picture can be sufficiently explained by a combination of ALS and FTD or whether ALS/FTD patients show a specific pattern of cognitive dysfunction, distinct from that reported in ALS and FTD alone.

**Disclosure:** Nothing to disclose.

## FW17-3

### ALS and FTD: genetics and phenotypes

V. Silani

*Milan, Italy*

ALS and FTD are since 2006 to be considered a single disease: the neuropathology first provided proof and genetics largely confirmed and contributed in defining this convergence. The discovery of TARDBP and FUS supported recognition that ALS and FTD represent overlapping clinical syndromes and this convergence has been further strengthened by the discovery of C9orf72, Ubiquilin 2 (UBQLN2) and other genes. It is now accepted that ALS constitutes a continuum with FTD, with pure ALS and pure FTD at the ends of this spectrum of motor neuron and frontotemporal neuron involvement. Intermediate phenotypes include ALS with cognitive impairment, ALS with behavioural impairment, and ALS-FTD. The clinical implications are so relevant both in the subgrouping of the patients and in the design of clinical trials that further investigations are highly needed for the most accurate definition of the cognitive and motor involvement in both the diseases. The overlap between ALS and FTD is indeed quite intricate, requiring to be identified according to the most updated neuropsychological testing (i.e. ECAS) in order to further address the most appropriate therapeutic strategies. C9orf72 mutations have been significantly reported in ALS with cognitive/behavioural changes and antisense oligonucleotide (ASO) therapy is now emerging as a highly promising approach. Of converse, a subgroup of FTD patients (10%) may show some sign of motor neuron degeneration, requiring prompt identification to define strategies to oppose weakness.

**Disclosure:** Nothing to disclose.